







Diagnostics and treatment of aggressive angiomyxoma

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Abstract

Aggressive angiomyxoma (AAM) is a rare benign soft tissue tumor that occurs predominantly in premenopausal women. Due to its nonspecific symptoms, AAM diagnosis may be challenging. The clinical diagnosis of AAM is challenging due to its rarity and nonspecific physical and radiological characteristics. Aggressive angiomyxoma can present manifestations similar to entities such as Bartolin cysts or angiomyofibroma. Histological examination shows a hypocellular and highly vascular tumor with a myxoid stroma containing cytologically bland stellate or spindle cells. The current gold standard of AAM treatment is surgical resection, with no difference in the recurrence rate observed for radical incisions. Aggressive angiomyxoma often stains positively for estrogen and progesterone receptors, leading to the exploration of gonadotropin-releasing hormone agonists as adjuvant or neoadjuvant therapy. The presence of chromosomal abnormalities, including translocation at the 12q13-15 locus involving the HMGA2 gene has been identified in AAM. Although AAM is benign and does not show potential for metastasis, its infiltrative nature in surrounding tissues and the high rate of postoperative recurrences warrant the use of the term 'aggressive.' Surgical resection remains the current gold standard of treatment, but the possibility of therapy using gonadotropin-releasing hormone agonists has emerged. Ongoing and future studies of AAM can potentially reveal the role of hormones in tumor growth and genetic mutations responsible for its development.

Keywords: aggressive angiomyxoma, soft tissue tumors, mesenchymal neoplasms, genitourinary tumors, pelvic tumors, vulvar tumors, pelvis, perineum, angiomyofibroblastoma, hormone receptor status, estrogen receptor, prostate receptor, rare tumors

Introduction

Aggressive angiomyxoma (AAM) is a rare benign soft tissue tumor that generally appears in the pelvic, perineal, genital, or inguinal regions. It occurs almost exclusively in women of reproductive age although it has been reported in patients aged from 16 to 70 years, with a peak incidence in the fourth decade of life. It has also been reported in men. It does not occur in children before puberty [1]. According to the litera-

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ture, 350 cases have been reported worldwide since the first report by Steeper and Rosai in 1983 [2]. More than 90% of patients described so far have been women [3]. It is a rare tumor whose exact pathobiology remains undetermined, but it has been reported that chromosomal translocation 12q13-15 results in overexpression of the high mobility group AT-hook 2 (*HMGA2*) gene [4]. Aggressive angiomyxomas are benign; their aggressiveness is related to the risks of local infiltration and the high rate of postoperative recurrences. Although it does not show the potential to disseminate, the tumor has an infiltrative capacity in skeletal muscle and adipose tissue [5–9]. The World Health Organization (WHO) defined AAM as a “tumour of uncertain differentiation” [10].

Aggressive angiomyxoma patients have nonspecific symptoms that lead to misdiagnosis. The rarity of the disease often causes delayed diagnosis, after surgical excision [2]. It is crucial to make a differential diagnosis in which magnetic resonance plays an important role [10]. In the case of AAM, wide surgical resection is the treatment of choice. Some cases showed that these tumor cells are characteristically positive for progesterone and estrogen receptors, suggesting a hormonal role in the development of this tumor. Therefore, gonadotropin-releasing hormone agonists are considered for adjuvant therapy. Despite its potential to infiltrate and recur, metastases are uncommon, and the overall prognosis is good [4, 10].

Epidemiology

Demographics

Aggressive angiomyxoma is a rare mesenchymal tumor that predominantly affects women of childbearing age (sex ratio F: M of 6.6:1). It is a rare neoplasm, as only about 350 cases have been reported so far, with only 24 cases affecting men. In female patients, there have been several reports of AAM during pregnancy. The age of the female patients ranged from 16 to 70 years, with a peak of around 35 years, and the age of the male patients ranged from 13 to 78 years. Aggressive angiomyxoma occurs more frequently in the pelvis and the perineum; This area accounts for more than half of all tumors (58%). Other localizations include vulva (21%), subcutaneous tissue (8%), inguinal region and scrotum (4%), oral soft tissue (3%), thigh (3%), sperm cord (2%), and umbilical cord (1%) [11]. As a result of asymptomatic tumor growth, AAM often develops over many years or even decades. In one of the cases we reviewed, a tumor in the scrotum was reported to have grown slowly for 20 years without any medical intervention and was the longest period reported [12]. Fetsch et al. [6] reported the largest number of patients in one research article:

29 women. When considered in a primary care setting, vulvar AAM is rare and misdiagnosis occurs in more than 80% of cases [13, 14].

Aggressive angiomyxoma has a low rate of metastases: metastases occur sporadically, and fewer than 10 cases have been reported with tumors metastasizing to the lung, larynx, and inferior vena cava. Blandamura et al. reported a case in which AAM lung metastasis was the cause of death [15–18]. However, no single metastatic case has been reported in men, which could be explained by the low number of men affected by this disease or different hormonal levels in male patients that make AAM completely benign in men [12].

Diagnostics

The clinical diagnosis of AAM is usually challenging due to its rarity, nonspecific radiological characteristics, and similarities with more common entities. Presentation is generally an asymptomatic soft tissue tumor that grows slowly over many years, eventually causing symptoms that prompt the patient to see a specialist. Aggressive angiomyxoma originally emerges from the soft tissues of the pelvis and the perineal region, but other locations were later confirmed as primary growth and described. Only three cases of AMM originating in the liver lobes have been reported. Without symptoms, the tumor can be detected incidentally during regular or intraoperative abdominal screening tests [19, 20]. Other unusual locations were depicted in the maxilla, axilla, chest wall, larynx, inside the upper part of the ureter, and even the lungs and the inferior vena cava; the last two were confirmed as metastatic lesions [15, 21–25]. Patients usually present with a painless swelling at a standard gynecological consultation or with a history of discomfort caused by the mass or even pressure effecting adjacent pelvic organs [26]. The visible part of the tumor usually represents only a fraction of the more extensive involvement of the deep soft tissue of the pelvis and retroperitoneum [4].

Due to the origin and tumor capacity, patients present various symptoms. Aggressive angiomyxoma originating in the perineal region is often associated with urinary discomfort, such as frequent urination or occasional stress incontinence [6, 27]. Other manifestations of urinary obstruction can be seen as progressively increasing voiding difficulties that involve initiating urination, incomplete bladder emptying, intermittent stream, and hematuria [24, 25, 28–33]. Dysuria and recurrent urinary tract infections were also observed in bladder tumors [2, 34]. The mass protruding from the perineal region can also be associated with obstruction of the vaginal canal and manifest as significant pain, severe menstrual pain, dyspareunia, and coital bleeding. It can be assumed to be vaginal

prolapse [35–39]. Patients with AAM arising from the gluteal region usually report a lump, lesion, or swelling that, on physical examination, is defined as soft to tender [8, 40–42]. Slowly progressing swelling of the gluteal region is mainly associated with dull pain, which may radiate into the lower limb, but can also stay asymptomatic during activities and manifest when the patient is seated or even reduce its size when the patient is lying down [16, 41, 43]. In the analyzed cases, patients with pelvic origin of the tumor are referred to specialists complaining of pelvic fullness, pressure, and pain [4, 33]. They describe difficulties in bowel and bladder function such as constipation, lower back pain during defecation, urinary frequency, and incontinence [6, 11, 30, 32, 33]. Painless swelling that extends from the groin may be primarily diagnosed as a femoral hernia, and bilateral leg edema may also be a clinical sign of AAM [15, 44].

In men, in whom AAM is very rare and is prone to occur in the scrotum and groin, patients usually report a slowly growing painless scrotal swelling similar to hydrocele, inguinal swelling, or symptoms of distinctive prostate enlargement such as intractable nocturia, urinary frequency, and urgency [12, 45–51]. Scrotal enlargement, abscesses, and other skin lesions can also develop [52]. On examination, scrotal tumors appear as a soft, nonfluctuant, nontransilluminant, and non-tender irreducible swelling that conforms to scrotal lymphedema, but without inguinal lymphadenopathy [46, 51, 53]. Generally, testes are within normal consistency and volume and are easily accessible [49, 52], but in severe cases, overgrowth makes it impossible to access testicles and even the penis [47]. A rectal exam may reveal AAM during benign prostate hyperplasia diagnostics [47].

Upon physical examination, the tumor presents a spectrum from soft and gelatinous, diffuse to tender and firm mass that can protrude into deeper parts of the body [37, 38, 44, 54]. Saadeh et al. [27] describe it as “consistent with fibroid enlargement of the uterus”. Tumors can be defined as spherical and mobile [10, 29, 33], elongated, and nonmobile [44, 55]. Sometimes, AAM appears as a well-circumscribed pedunculated or polypoidal mass [7, 37, 56]. The skin surrounding the tumor usually remains within the normal range as smooth and intact [57], but in some cases, brown pigmentation [35] and ulcers accompanied by pruritus were described [58]. Patients may report numbness [55]. In severe cases, the lesion can extend externally, creating an irregularly shaped, well-circumscribed, pedunculated mass [58] or blocking the introitus, making it impossible to perform the examination correctly [59].

Aggressive angiomyxomas vary in size and form. The smallest detected and confirmed lesions were > 1 cm [36]. The largest known tumor that occurred in

a woman was described in 1998. It measured 57 × 47 × 23 cm and had slowly developed over approximately 8 years [60]. On the other hand, the largest male lesion had a circumference of 106 cm and a weight of almost 30 kg [47].

As mentioned before, physical examination of the tumor usually reveals only a fraction of the involvement of the deeper parts of the adjacent tissues. However, radiology enables proper estimation of dimensions, location, and infiltration. Aggressive angiomyxoma has nonspecific features on radiographic images, so it is often misdiagnosed as a more common disease entity. The final diagnosis is always established by histopathology. The most commonly used in perineal imaging is ultrasonography (USG). Ultrasonography usually shows a hypoechoic and heterogeneous mass, with well or ill-defined margins consisting of cystic and solid components [42]. On color Doppler ultrasound, a blood pattern of abundant and external vessels can be visualized [61]. However, irregular and randomly dispersed vessels may appear in the central area of the tumor [20]. Color Doppler flow imaging may also reveal predominately low resistance type arterial blood flow [29]. Transvaginal USG is not used as often as external USG but can also reveal the solid nature of the lesion and increased vascularity. Aggressive angiomyxoma may be taken for a cyst or polyp [38]. In males, the scrotal USG usually shows a well-defined solid heterogeneous hypoechoic mass with high vascularity [49] and no evidence of infiltration of the testes. Due to rare occurrences in the prostate, the transrectal USG (TRUS) is also valuable for visualizing lesions [30]. Imaging also plays an additional role in AAM. Diagnosis. Precise needle biopsies are performed safely under computed tomography (CT) or USG guidance and usually confirm a presumptive diagnosis based on characteristics in histopathological images [3, 15, 26, 40, 62].

Computed tomography imaging typically shows an enhanced mass that is iso- or hypo-attenuating related to muscle with swirled enhancing tissue internally [3] or demonstrates both cystic and solid components [10]. The border between the tumor and the adjacent tissue may be indistinct, indicating the infiltrative nature of AAM. Contrast-enhanced CT scans reveal heterogeneous, well-defined masses in the case of metastases described by Geng et al. [15].

Magnetic resonance imaging (MRI) not only helps assess the extent of the tumor for surgical planning but also makes the extension across the pelvic diaphragm easily visible, helping to plan resection [26] (Fig. 1). Magnetic resonance imaging reveals hypo- to iso-intensity compared to muscle in T1 weighted images (T1WI) iso- to hyper-intensity in T2WI and fat-suppressed in T2WI [42, 62]. Hyperintensive images on the T2 sequence are likely related to high water

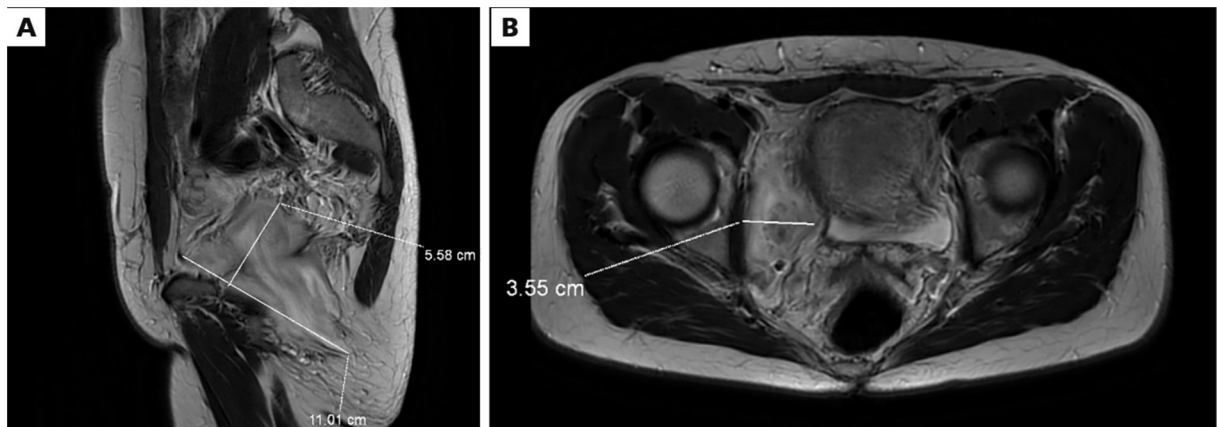


Figure 1. Advanced aggressive angiomyxoma (AAM) in the ischio-anal fossa on the right side of the pelvis. Magnetic resonance imaging (MRI), T1 weighted sagittal image (A) and transverse image (B)

content and a loose myxoid matrix [9]. Aggressive angiomyxoma intensifies after contrast administration, probably due to high internal vascularity, demonstrating a characteristic, but not specific, swirling or layering appearance in post-contrast images [42], which is a result of enhancement of the tumor fibrovascular stroma and is described in almost 83% of cases [63]. Swirled architecture and lower signal intensity can also be seen in T2WI without intravenous contrast [3]. Magnetic resonance imaging also allows for monitoring of the tumor response during the eventual neoadjuvant treatment. It is especially convenient in postoperative follow-up to detect even small lesions, which may suggest residual disease or local recurrence [3, 38].

Diffuse weighting imaging (DWI) is rarely used in preoperative AAM investigation; therefore, only two cases include a description of its image. Aggressive angiomyxoma appeared to show a heterogeneous high signal intensity on the b0 and b1000 sequences. The typical architecture was observed only at the b0 sequence; however, it disappeared as the b value increased and on apparent diffusion coefficient (ADC) mapping imaging even in a mass more than 10 cm in diameter. Apparent diffusion coefficient also shows a high value in the tumor estimated at $2 \times 10^3 \text{ mm}^2/\text{sec}$, comparable with ADC in myxoid tumors. The persistence of a high-intensity tumor signal on this imaging with a high b0 value may suggest the possibility of an easy and earlier relapse diagnosis using DWI sequences [3, 62]. However, there are not enough case series to support this thesis.

Positron emission tomography (PET) scan may be performed to detect lymphadenopathy or metastatic disease, while cases of AAM are usually a singular lesion without other tumors [64]. Therefore, the appearance of AAM on PET has rarely been described. In cases with PET scans performed, the tumor did not show any fludeoxyglucose (FDG) uptake or

a hypermetabolic state in the mass that could permit differentiation between benign and malignant conditions [19, 30].

The ability to visualize AAM is not limited to the previously mentioned ways, but due to the uncommon origin of some tumors, other methods are used to make diagnosis. A conventional vascular angiogram can be performed and usually reveals a hypervascular mass [42]. The mass in the perineum and its relationship to the anal canal can be assessed with a 3 dimension (3D) anal USG [65]. A tumor may also be investigated with USG enhanced with liver sonazoid, as performed by Sato et al. [19], who revealed a solid hypovascular mass with an improved internal partition wall. Tumors that arise in the urinary tract can be visualized by urologic CT, flexible cystoscopy, or cystourethroscopic examination [2, 24, 48].

Pathological characteristics

On gross examination, AAM is described as lobular and may present as an encapsulated or unencapsulated mass but with a relatively well-circulated border. As mentioned earlier, size can range from less than 1 cm in diameter to 106 cm in circumference [36, 47]. It has a soft to rubbery or gelatinous consistency. The cut surface has a relatively homogeneous, glistening, grey-white, or pink-tan color with no areas of necrosis or hemorrhage. The appearance may also be edematous and contains microcysts filled with myxoid material [5, 36, 52, 66].

Microscopic examination of AAM reveals a paucicellular neoplasm predominately composed of stellate to spindle-shaped fibroblastic cells with ill-defined cytoplasm and bland cytology embedded in a loosely collagenized myxoid stroma [6, 37]. Sometimes, the stroma is positive with alcian blue, indicating an eosinophilic background [48, 50, 56]. The nuclei are round to oval, bland with one or two small

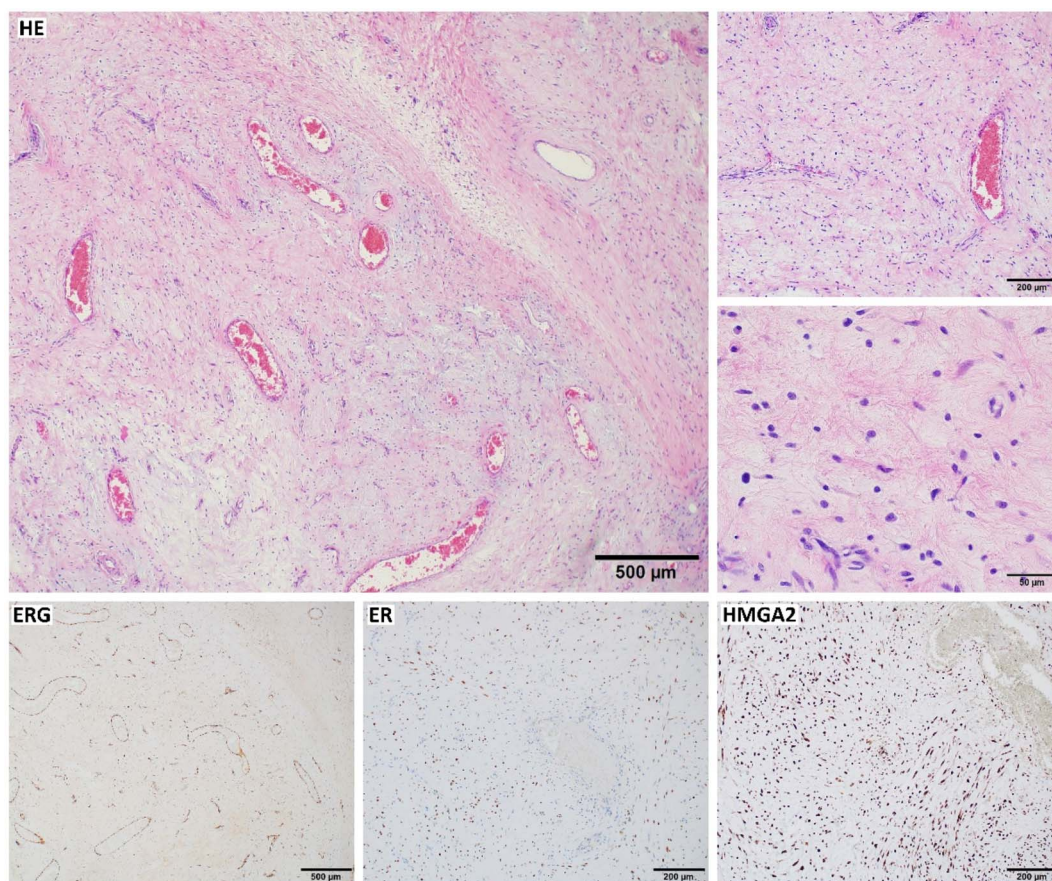


Figure 2. Deep aggressive angiomyxoma is paucicellular, composed of bland spindle cells; stroma is abundant and myxoid with prominent vessels (HE); the vessels are positive in ERG staining; tumor cells express estrogen (ER) and progesterone receptors and show HMGA2, which is helpful in routine histopathological diagnostics

nucleoli with exceptional mitotic figures, but never with nuclear atypia [1, 56]. An abundant myxoid matrix haphazardly contains several thin and thick-walled vessels of different sizes, with perivascular hyalinization and vascular hypertrophy of the more peripheral venules [5, 44]. Tumor cells are sparsely distributed except in the perivascular area, where they aggregate around vessels [10, 35]. The tumor commonly infiltrates adjacent tissues, resulting in entrapped fragments of fatty tissue, peripheral nerves, or skeletal muscles [3, 39]. Occasionally, findings may include extravasated red blood cells, mast cells, or lymphocytes [22, 38, 57, 67].

Aggressive angiomyxoma does not have a specific immunohistochemical marker but expresses a characteristic pattern of markers. This tumor positively stains for vimentin and, in some exceptional cases, for desmin. The most negative desmin staining came from tumors in odd locations such as the maxilla, liver, or prostate. Most AAM tumors also show immunopositivity for CD34, smooth muscle actin (SMA), and muscle-specific actin (MSA). Reactivity for S100, cytokeratins, and CD117 is generally negative. Tumor tissues are characteristically immunoreactive for

estrogen receptors (ER) and progesterone receptors (PR) irrespective of sex; however, in males, ER are usually absent or tissues are reactive for androgen receptors (AR) [48, 51]. The Ki67 index generally shows residual proliferation (< 1% of tumor cells); however, it can vary from 2% to even 10% [11, 21, 39]. HMGA2 is a sensitive biomarker but not specific; CDK4 could also be positive without overexpression of MDM2 (Fig. 2).

Differential diagnosis

Aggressive angiomyxoma occurs primarily as a vulvar or vaginal soft mass, which is frequently mistaken for a Bartholin duct cyst, lipoma, Gardner duct cyst, vaginal cyst, vaginal or vulvar abscess, vaginal prolapse, or perineal hernia [3, 5, 63]. In men, the prompt diagnosis is usually inguinal hernia or hydrocele [8, 12, 45]. The features of AAM can also be confused with other soft tissue tumors such as angiomyofibroblastoma, superficial angiomyxoma, cellular angiofibroma, angiomyolipoma, dermatofibrosarcoma protuberans, superficial myofibroblastoma, myxoid neurofibroma, myxoid lipomatous tumors, or myxoid

leiomyoma, or even gastrointestinal stromal tumor. Clinical examination rules out infectious and inflammatory diseases such as abscesses, and morphological imaging, such as computed tomography, confirms the absence of hernia, prolapse, or myoma. Bartholin, Gardner, and vaginal cysts show significant enhancement only if infected; in this case, MRI scans usually show peripheral enhancement of the variably thick wall of the cyst, which is easily distinguishable from the AAM enhancement pattern [3].

The main differential consideration for AAM is angiomyofibroblastoma (AMFB). This rare benign mesenchymal tumor arises almost exclusively from the vulvovaginal region in women but may also occur in the inguinoscrotal region in men. AMFB shares many features with AAM, such as location, age at presentation, clinical manifestation, pathology, and immunohistochemistry (IHC) entities. Angiomyofibroblastoma is well circumscribed, usually has a smaller volume of less than 5 cm³, and affects only superficial tissues [9, 16, 68]. Histologically, it shows much higher cellularity and has a less noticeable myxoid stroma with more numerous blood vessels. Cells are plumper or short-spindle-shaped compared to AAM and appear to be typically concentrated in the areas surrounding the vessels, which are typically venular or capillary-sized and delicate [69–71]. When vessels are less prominent in AMFB, histopathological features display overlapping; therefore, a thorough examination is critical for final diagnosis.

In contrast to AMFB, AAM is more infiltrative and has a higher probability of local recurrence [1, 6, 29]. Aggressive angiomyxoma requires a wide local excision given the infiltrative nature of the lesion in contrast to the simple excision of AMFB; therefore, it is important to differentiate these two diseases before surgery. On ultrasound, AMFB shows hyperechoic areas with irregular and small hypoechoic cystic areas interspersed within homogeneous echogenic stroma. Aggressive angiomyxoma is typically a hypoechoic mass with homogeneous echogenicity and occasional echogenic septa, which can create a layered or swirled appearance similar to that seen on magnetic resonance imaging or CT. The vascularity seen on the Doppler color imaging is much more prominent in AAM due to the predominant capillary component of AMFB [61, 72]. Magnetic resonance imaging may be valuable with in-phase and opposed-phase sequences showing microscopic fat inside the AMFB [3]. Aggressive angiomyxoma differential diagnosis needs to cover:

- a) superficial angiomyxomas (cutaneous myxoma) arising in the dermis or subcutis are often located in extragenital sites, such as the head and neck. However, they can also be associated with the vulvovaginal area. On gross examination, the

superficial angiomyxoma has a distinct lobular or multinodular architecture. Histologically, they are both characterized by myxoid features, with moderate to sparse cellular populations of stellate and spindle-shaped cells, but superficial angiomyxoma lacks large caliber vessels such as those in AAM and is generally negative for ER and PR [6, 12, 16];

- b) cellular angiofibroma (CA) is a rare benign mesenchymal tumor affecting superficial soft tissues of the vulvovaginal region in women and the inguinoscrotal region in men. It is characterized by small size, well-circumscribed margins, and asymptomatic onset. On the other hand, AAM tends to be a large, deep-seated mass with infiltrated borders and entrapment of surrounding tissues. CA comprises bland spindle cells that proliferate in an edematous to fibrous stroma with small to medium thick-walled, often hyalinized vessels and a moderate number of inflammatory cells comprising lymphocytes and rarely neutrophils. Immunohistochemistry shows a similar pattern to AAM; however, CA has poor stains for desmin and alpha-SMA [73];
- c) dermatofibrosarcoma protuberans (DFSP) usually occur in young to middle-aged adults involving the trunk and proximal extremities, but in rare cases, the vulvar region. The myxoid variant shows a varying degree of myxoid change to its stroma, often resulting in the loss of the characteristic storiform growth pattern of classic DFSP and the increased prominence of small to medium blood vessels. Dermatofibrosarcoma protuberans and AAM are CD34 positive; however, AAM is generally desmin positive and expresses hormone receptors. In challenging cases, fluorescence *in situ* hybridization (FISH) and reverse transcription polymerase chain reaction (RT-PCR) can help detect the peculiar *COL1A1-PDGFB* in DFSP [74, 75];
- d) superficial myofibroblastoma (SMF) is a rare benign mesenchymal tumor that arises in the vulvovaginal region. It shares many entities with AAM, such as an expansive growth pattern and a histological image with the immunohistochemical pattern; however, clear margins and superficial localization lead to SMF diagnosis. Due to its superficial location, SMF frequently presents edema and a massive myxoid change in the stroma, which cannot exclude the diagnosis of AAM. Superficial myofibroblastoma blood patterns tend to concentrate in the central region of the lesion and consist of small to medium-sized vessels; thick, muscular, or hyalinized walls are seldom seen [76];
- e) Other myxomas, myxoid liposarcomas, and myxoid neurofibromas must also be considered in the

differential diagnosis of AAM. Myxomas, usually located intramuscularly, are rare in the pelvic regions, while AAM can adjoin but do not invade the pelvic musculature. They are less cellular and have sparser vasculature than AAM [6, 9]. Due to its infiltrative nature, AAM may entrap adipose tissue, appearing similar to rare lipomatous tumors with spindled or stellate mesenchymal components. Myxolipoma and angiomyxolipoma, which have more vascular components, mainly consist of adipose tissue. Myxoid liposarcoma mostly appears in the lower extremities and demonstrates abundant lacy or linear adipose tissue that contains well-organized lipoblasts and arborizing capillary networks. Fluorescence *in situ* hybridization analysis to amplify the *MGM2* gene may be valuable in confirming diagnosis [4, 6, 9, 16, 77]. Myxoid neurofibroma is hypocellular, has a prominent vasculature, and contains a small number of Schwann cells. Tumor cells are spindle-shaped with wavy or buckled nuclei and show diffuse immunoreactivity for S-100 [6, 78];

- f) myxoid leiomyoma is a benign smooth muscle tumor associated with the uterus and pelvic region. It can appear in large sizes and histologically contain abundant myxoid material between smooth muscle cells. Spindle-shaped cells contain more abundant eosinophilic cytoplasm than AAM [16];
- g) gastrointestinal stromal tumor (GIST) rarely arises in the pelvic region and, if so, usually causes nonspecific symptoms. CT image shows a well-circumscribed soft mass with heterogeneous density, which may mimic AAM; however, low attenuation parts may suggest necrosis or hemorrhage. It consists of fascicular spindle-shaped cells with the characteristic pattern of IHC, which differs from AAM by positive staining for CD117 and DOG-1 [79].

Solitary fibrous tumors (SFT) are rare spindle cell neoplasms with fibroblastic differentiation that may occur throughout the body but commonly develop in the pleura. Histologically, they are hypercellular and composed of elongated spindle cells arranged in a haphazard pattern and surrounded by prominent branching vasculature. Imaging differentiation is challenging due to the common entities with AAM, even with characteristic “swirl” patterns. SFTs have a characteristic inversion of the long arm of chromosome 12, which produces the NAB2-STAT6 fusion protein [77]; CD34 and STAT6 are the immunostainings detected the most frequently.

Genetics

The genesis of AAM is still under investigation, but several genetic abnormalities have been reported.

Typical genetic events found in AAM are aberrations in the 12q14-15 chromosome region, a phenomenon also observed in various tumors, including lipomas, uterine leiomyomas, and pulmonary chondroid hamartomas. These genetic alterations are not specific to AAM. Most abnormalities relate to the *HMGA2* gene (previously designated *HMGIC*) located in the 12q15 chromosomal region 12q15, which is a gene encoding a member of the high mobility group of proteins. A notable example is the pericentric inversion $inv(12)(p11.2q15)$ that led to the discovery of an ectopic sequence derived from an *HMGA2* fusion transcript in AAM. With the use of FISH examination experiments, researchers were able to confirm that the same chromosomal region 12p11.2 is involved in lipomas, AAM, and pulmonary chondroid hamartomas (PCHs) with $inv(12)(p11.2q15)$. In particular, the intensity of the signal at 12p was significantly stronger than at 12q within the hamartoma and some lipomas, indicating the presence of two distinct breakpoint clusters. These findings shed light on the intricate genetic underpinnings of aggressive angiomyxoma and its relationship with other tumor entities with *HMGIC* abnormalities [52, 67, 80].

Rawlinson et al. [33] analyzed 20 metaphase cells, and these molecular analyses revealed translocations within the 12q13–15 region involving the *HMGA2* gene. This gene belongs to a family of transcriptional factors that are typically inactive in adult tissues but are involved in embryogenic development. Bicolour FISH analyses have confirmed these translocations, such as the translocation 46, XX,t(12;21)(q15;q21.1) translocation 46, XX,t(12;21)(12;21)(q15;q21.1) observed in all examined cells. FISH studies also revealed rearrangements in the *HMGA2* gene locus, aligning with *HMGA2* overexpression findings in immunohistochemical analyses. These chromosomal translocations within 12q13-15 have also been reported in other mesenchymal neoplasms, such as lipomas, liposarcomas, leiomyomas, and pulmonary hamartomas. This commonality suggests a shared molecular genetic background among these tumors [3, 33].

Despite these genetic insights, the etiology of AAM remains elusive. Cytogenetic studies have also revealed the loss of X chromosomes in a significant proportion of AAM cells, suggesting its role in tumor formation. Consequently, chromosomal alteration $t(8;12)$ is emerging as a valuable tool for identifying residual disease in AAM, shedding light on its intricate genetics and potential therapeutic targets [50, 51]. Genetics of AAM support a shared molecular background with other mesenchymal tumors and highlight the potential utility of cytogenetic, FISH, and immunohistochemical studies in identifying AAM.

Treatment

Treatment of locally advanced disease

Surgery is the primary modality in the treatment of locally advanced aggressive angiomyxoma, supplemented by adjuvant hormonal therapy involving agents such as tamoxifen, raloxifene, or gonadotropin-releasing hormone (GnRH) analogs. The analyzed publications introduce a nuanced discourse in which divergent perspectives exist on the optimal surgical approach. Diverse surgical approaches affect the rates of aggressive recurrence of angiomyxoma, adding a layer of complexity to the therapeutic decision-making process. The therapeutic utility of chemotherapy and radiotherapy is limited due to the low mitotic activity observed in tumor cells. Alternative therapeutic modalities may be vessel embolization; however, it should be noted that AAM frequently manifests itself with numerous feeding vessels [4, 8, 9].

Preoperative preparations involve imaging examinations to assess the extent of the tumor and aid in surgical planning. Magnetic resonance imaging is commonly employed for planning surgical approaches, ensuring complete excision while preserving proximal structures such as the urethra, vagina, sphincters, etc., and local and pelvic nodal staging. Computed tomography or PET/CT scans are also used to check for any signs of the disease spreading to distant areas. Hormonal therapy (with GnRH analogs, tamoxifen, and raloxifen), including aromatase inhibitors, and vessel embolization (in one case) are used to reduce tumor size [9, 26, 64]. Of the 59 surgically managed cases, 20 underwent wide excisions. Six cases involved laparotomy, while ten were approached abdominally, perineally, or through a combination of both. Hysterectomy with bilateral salpingo-oophorectomy was performed in 4 cases. Scrotoectomy was performed in 3 men. Lymphadenectomy was required in two cases of surgical treatment [24]. In one instance, a urethrectomy was necessary and a total pelvic exenteration was performed for a colossal 28-kg tumor. Transurethral resection of the bladder tumor (TURBT) [2] was performed once and transurethral prostate resections were performed twice in AAM patients [48, 50]. Lastly, there was a unique case of AAM of the larynx, approached transorally [3–11, 16, 20–25, 27–30, 32–35, 37–42, 44, 46, 47, 52–59, 66, 67, 69, 78, 81–87].

According to reports, AAM recurrence of AAM can happen between 2 months and 15 years after radical surgery. Recurrence of AAM takes place mostly after > 5 years, which emphasizes the need for prolonged postoperative follow-up. Although some studies support the hypothesis that wider resection margins contribute to a reduced recurrence rate, other studies show that the extent of resection margins

does not affect the recurrence rate. The reported recurrence rates of AAM are between 10 and 85% after 5 years. In selected studies, 40% and 50% recurrence rates were reported for wide and regular resections [42], respectively. Another study reported 0% recurrence after wide resection and 30% after regular resection [52], while other authors reported recurrence from 47% [9] to 71% [11] and 85% after three years [3, 4, 8, 10, 16]. Significantly, a study showed a decreasing trend in recurrence, dropping from 75% to 10–30% over the last 20 years. This improvement was attributed to advances in treatment and diagnostic capabilities over time [3].

Aggressive angiomyxoma treatment has evolved to include hormonal therapy, given the prevalence of the tumor in premenopausal women and its positive ER and PR status. Although surgery remains the standard approach, hormonal therapy, particularly with GnRH agonists (including in male patients), is considered an alternative, both in primary and adjuvant settings, even in recurrent cases. GnRH agonists, although promising according to some studies, have potential drawbacks, including menopausal symptoms and bone loss. These agonists initially stimulate the release of follicle-stimulating hormone (FSH) and luteinizing hormone (LH), leading to increased levels of estrogen and progesterone. However, prolonged treatment results in down-regulation of the receptor and decreased hormone levels, contributing to tumor resolution. Some propose the integration of GnRH agonists into treatment protocols to potentially avoid radical pelvic surgery in hormone receptor-positive patients. Various hormonal therapies, such as raloxifene, tamoxifen, and GnRH analogs, are used to shrink tumors before excision and manage recurrences. However, it is important to note potential side effects, including significant osteoporosis or depression. Although there are isolated reports of successful AAM treatment solely with GnRH agonists, there is a trend toward less invasive treatments in the literature analysis [3, 4, 8, 9, 11, 81] (Fig. 3).

Radiation therapy

The role of radiation therapy in AAM remains controversial. Perioperative radiation therapy data provide mixed results. Adjuvant radiation therapy, typically administered at a dose of approximately 60 Gy, has been considered a potential therapeutic strategy for AAM, particularly in cases with positive surgical margins. The benefit of preoperative external beam radiotherapy in AAM remains uncertain due to its slow growth rate, which limits its use to only marginally resectable locally advanced tumors. Radiotherapy becomes a valuable consideration in patients who do not respond to hormone therapy or embolization or for whom extensive surgery is deemed necessary [10, 21, 30, 37, 50, 51, 88]. Han-Guerts et al. propose that

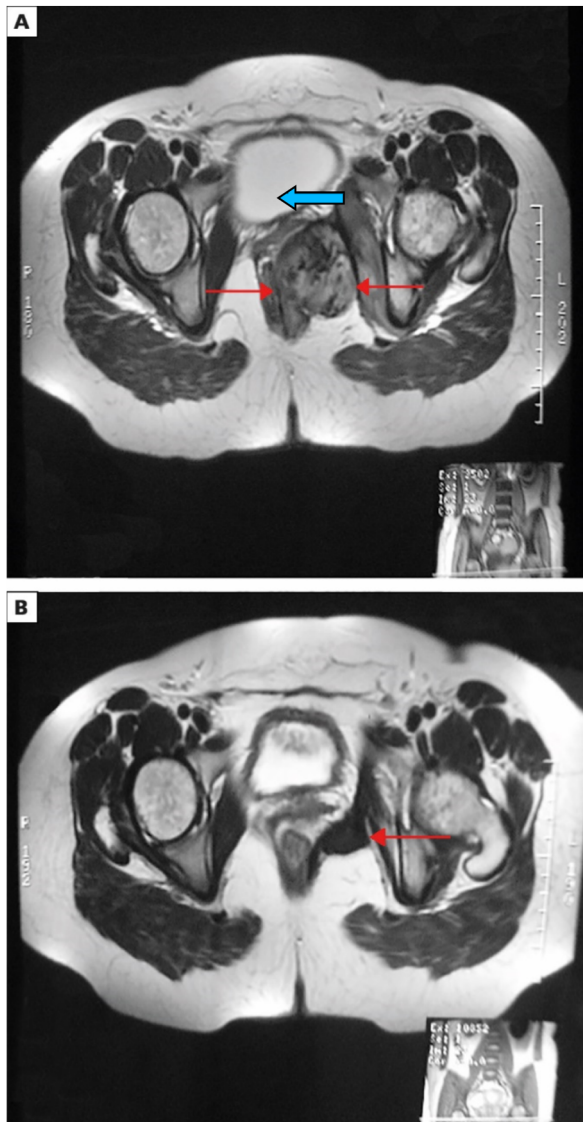


Figure 3. Nearly complete response of pelvic angiomyxoma to hormone therapy. Magnetic resonance image before (A) and after (B) 12 cycles of leuprolide

radiotherapy should be reserved for cases resistant to treatment yet still experiencing symptomatic disease [3, 7, 9, 11, 55, 81].

Treatment of metastatic disease

Aggressive angiomyxoma is an extremely rare tumor characterized by its slow growth rate and low metastatic potential. Although it has a propensity to invade nearby structures, metastasis rarely occurs. However, isolated cases of AAM with distant metastases have been reported, with some patients succumbing to the disease. Sometimes, AAM can manifest as multiple masses although this presentation is rarely documented. Imaging studies, including CT and MRI, have been instrumental in diagnosing AAM and evaluating its extent. In particular, AAM

can cause mass effects, displacing adjacent normal tissues. Ultrasound plays a crucial role in assessing nodal involvement, particularly in the context of vulvar cancer, where lymphatic drainage is extensive. High-resolution MRI has shown promise in detecting and characterizing inguinal and pelvic lymph nodes, improving the precision of lymph node evaluation. Computed tomography imaging can identify the primary tumor and assess pelvic lymphadenopathy and distant metastases. Positron emission tomography/computed tomography is valuable for detecting lymphadenopathy or metastatic disease, with reasonably high sensitivity and specificity [9–11, 15, 55, 61].

Following treatment, long-term surveillance is essential due to the potential for late recurrences, which highlights the importance of regular cystourethroscopy and annual MRI. A definitive gold standard treatment with such limited reported metastatic cases has not yet been established. However, the surgical approach coupled with adjuvant radiotherapy has consistently demonstrated its value in the management of this condition. Postoperative radiation and GnRH agonists have shown efficacy in the treatment of metastatic AAM, providing valuable treatment options for these rare cases. This multifaceted approach combines clinical, imaging, and therapeutic strategies to address the complex nature of aggressive angiomyxoma, ensuring comprehensive patient care [3, 10].

Palliative care

Although a relatively indolent course typically characterizes AAM, instances that require palliative care have occasionally been documented. In particular, one of these cases involved a recurrent AAM that demonstrated extensive vascular invasion, encompassing the inferior vena cava and the right atrium, which was accompanied by pulmonary metastases. A multidisciplinary surgical approach was used to facilitate the patient's distressing symptoms. However, the formidable intraperitoneal and extraperitoneal mass proved challenging to excise due to its encapsulation of vital structures, including the ureters, urinary bladder, and colon [15].

Summary

This comprehensive review addresses the challenges of diagnosing AAM, a rare benign soft tissue tumor that predominantly affects premenopausal women. Our review highlights the complexity of clinical diagnosis due to nonspecific features, often similar to other conditions. Histologically characterized by a myxoid stroma with bland stellate or spindle cells, AAM is deemed “aggressive” due to its infiltrative nature and high postoperative recurrence rates. Surgical resection is the current gold standard treatment,

but ongoing research explores the potential benefits of gonadotropin-releasing hormone agonists. Positive staining for ER and PR and identifying chromosomal abnormalities further contribute to understanding AAM. Despite its benign nature, this review emphasizes the need for more research to unravel the genetic basis, hormonal influences, and potential therapeutic targets for this rare tumor.

Article Information and Declarations

Author contributions

A.M., K.B., M.S., M.W.: data collection, draft manuscript preparation; A.M.C., P.R.: study conception and design, data collection, draft manuscript preparation; A.S.-Ć.: data collection, draft manuscript preparation, figures; T.Ś.: study conception and design, data collection, draft manuscript preparation, figures.

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Conflict of interest

All authors declare no conflict of interest.

Supplementary material

None.

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